Effects of Paternal Occupational Exposure on Spontaneous Abortions

ABSTRACT

Background: Paternal exposure to mutagenic agents has been suggested to affect pregnancy outcome adversely.

Methods: A nationwide data base of medically diagnosed spontaneous abortions and other pregnancies and national census data was used to evaluate the effects of men's occupational exposures on risk of spontaneous abortion in 99 186 pregnancies in Finland. Census data from the years 1975 and 1980 provided information about the occupation, industry, and socioeconomic status. A job-exposure classification was developed to classify women and their husbands according to possible occupational exposures on the basis of their occupational title and industry.

Results: In 10% of the pregnancies, the husband was exposed to one or more of the mutagens, and the rate of spontaneous abortion was unaffected (OR = 1.0). Of the 25 specific mutagenic exposures evaluated, paternal exposure to four (ethylene oxide, rubber chemicals, solvents used in refineries, and solvents used in the manufacturing of rubber products) was associated with an increased relative risk of spontaneous abortion. In addition, the risk of spontaneous abortion was higher among wives of rubber products workers than among unexposed men.

Conclusions: Although there is some biological rationale for the findings of this study, these findings need to be confirmed by studies in which individual exposures can be measured directly. (*Am J Public Health*. 1991;81:1029–1033)

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Introduction

In animals paternal exposure to mutagenic compounds can increase the rate of spontaneous abortions.[1] In humans, however, this relationship remains unclear. For vinyl chloride,[2] anesthetic gases,[3] dibromochloropropane,[4] chloroprene,[5] smelter work,[6] waste water exposures,[7] and organic solvents,[8] effects have been suggested, but the data either have been contradictory or remain unconfirmed. An association has also been found with some paternal occupations: metal-plate and constructional steel workers, crushers and grinders, sewers, workers caring for fur-bearing animals,[9] and mechanics and repairers of motor vehicles.[10]

Several methodologic issues must be considered in conducting studies concerning male effects on reproduction. First, such studies must take into account maternal factors. Second, they should collect data on pregnancy outcomes which minimize systematic bias. Third, they need large enough numbers of exposed men to provide reasonable statistical power. We attempted to address these issues in studying the effects of male occupational exposures on the outcome of pregnancy by using data from two national censuses and a nationwide data base of medically diagnosed pregnancy outcomes. Exposures were determined indirectly by using a job-exposure classification. This large dataset can be used to generate hypotheses for other studies of the effects of occupational exposures on reproductive outcomes.

Methods

Data on reproductive outcomes and maternal age were obtained from the nationwide Hospital Discharge Register (HDR) and from hospital clinics. We collected data on all women with a diagnosis of spontaneous abortion (ICD-8 codes 643 and 645), induced abortion (ICD-8 codes 640–642) and birth (ICD-8 codes 650–662) between 1973 and 1982. A separate questionnaire was sent to the hospitals to collect information on patients treated on an outpatient basis and not registered in the HDR. The content, technical quality, and reliability of the data base of medically diagnosed pregnancies have been described elsewhere.[11]

Information on the occupation and industry of women and their husbands and the women's socioeconomic status was obtained from the 1975 and 1980 national censuses of the Central Statistical Office of Finland. Pregnancy data for the years 1973 to 1978 were linked to the 1975 census, and the data for the years 1979 to 1982 to the 1980 census.

In the census of 1975, performed on December 31, 1975, occupational information was requested as follows: "Occupation in the place of employment" with the instruction "State your occupation as accurately as possible, not only by hon-

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TABLE 1—Pregnancy Outcomes Among Wives and Adjusted[a] Odds Ratio of Spontaneous Abortion for Paternal Exposure to Mutagenic Agents

Husband's Exposure Status	Spontaneous Abortions	Induced Abortions	Births	All Pregnancies	Odds Ratio	95% Confidence Interval
Not exposed[b]	7772	7029	72 815	87 616	1.0	
Potential, low exposure	820	1045	8065	9930	1.0	0.9 – 1.0
Moderate or high exposure	139	151	1350	1640	1.0	0.9 – 1.2

[a]Adjusted for age (≤24, 25–29, 30–34, 35–39, ≥40); socioeconomic status (1 = employers, own-account workers, upper level employees, 2 = lower level employees, students and pupils, 3 = manual workers); maternal exposure to reproductive hazards (not exposed, exposed).
[b]Referent category.

orary titles or degrees." In the census of 1980, performed on November 1, 1980, the question was, "In which occupation did you work for the longest period during the last 12 months?" Occupations were coded by census officials, on the basis of the Nordic Classification of Occupations and the International Standard Classification of Occupations. Industry was coded on the basis of the Finnish Standard Industrial Classification.

We classified the occupational exposure status of men and women on the basis of occupation and industry, using a job-exposure classification developed in cooperation with two experienced industrial hygienists. The job-exposure classification is organized by job groups, which are combinations of occupation and industry having a similar type of exposure. For each job group a list is given of agents suspected of having adverse effects on reproduction. The assessment of the exposures among the job groups was based on the industrial hygienic measurements made by the Institute of Occupational Health[12,13] and the Finnish register of employees occupationally exposed to carcinogens (ASA Register).[14]

The list of potentially dangerous agents in the classification comprises 78 exposures, including separate chemical substances (e.g., benzene, ethylene oxide), mixtures of exposures (e.g., mixtures of solvents or metals), and nonspecific exposure groups (e.g., biologic factors, rubber chemicals, pesticides). Twenty-five of the 78 exposures were suspected mutagens, based mainly on the classification of the International Agency for Research on Cancer.[15]

Three levels of exposure were distinguished according to the results of industrial hygienic measurements and the prevalence of exposure in the job group: "moderate or high," "potential, low," and "none." "Moderate or high exposure" included jobs in which the level of exposure to mutagens was continuously at least half of the Threshold Limit Value (TLV) or higher or in which the exposure periodically exceeded TLV and the prevalence of exposure was high. "Potential, low exposure" denoted either (a) jobs with low level but high prevalence of exposure to mutagens, (b) jobs which lacked industrial hygiene measurements but which were reported to the ASA Register, or (c) jobs with a high level and unknown prevalence of exposure.

The susceptible time period was determined on the basis of the time of conception and the time period for which the two censuses obtained information on occupation. For men, the time of spermatogenesis (80 days before conception) was defined as the relevant time period for exposure; for women, the relevant time period was considered to be the first trimester of pregnancy. The analysis of exposure to any mutagenic agents was limited to the pregnancies terminated between January 1, 1976, and December 31, 1976, and between May 1, 1980, and April 30, 1981. In the analysis of specific mutagenic exposures we used a 2-year period close to the census, i.e., January 1, 1976, to December 31, 1977, and May 1, 1980, to April 30, 1982, because the number of workers exposed to a specific agent was often small.

After the pregnancies of women less than 12 and more than 50 years of age had been excluded as well as those with unspecific data on men's and women's occupation, industry, or socioeconomic status, the study population included in the analysis for the limited time periods of January 1 to December 31, 1976, and May 1, 1980 to April 30, 1981, comprised 99 186 pregnancies.

The risk odds ratios comparing the odds of spontaneous abortion for paternal exposure to a mutagen with the odds of spontaneous abortion for the nonexposed group were obtained by using linear logistic regression analysis.[16] To minimize random error in the effect estimates, low and moderate or high levels of exposure were combined if the number of the workers in either category was too small. Age, socioeconomic status, and maternal exposure to potential reproductive hazards were included in the models to control for the confounding effect of these variables. To gain precision, odds ratios were only adjusted for age if fewer than 100 pregnancies occurred among the workers exposed to a chemical. The exclusion of socioeconomic status in the model did not significantly change the odds ratios for these exposures. Maximum likelihood estimates of odds ratios, which were used as surrogate measures of relative risks, and their 95% confidence intervals were calculated by using the GLIM computer program.[17] Odds ratios for exposure to mutagens were similar regardless of whether induced abortions were included or excluded from the denominator. In calculating the rate of spontaneous abortion, we included births, spontaneous abortions, and induced abortions in the denominator. (Although it is common in the literature to refer to these measures as rates, they are in fact proportions or risks because they are calculated by dividing the number of spontaneous abortions by the total number of pregnancies.[16])

Results

The rate of spontaneous abortion in the study population was 8.8%, which is nearly the same as the rate among all Finnish women (8.9%).[11] Of the husbands, 10% were considered to have low or potential occupational exposure to mutagenic agents and only 1.7% were classified as heavily exposed (Table 1). After adjusting for maternal age, socioeconomic status, and maternal exposure to reproductive hazards, the odds ratio of spontaneous abortion did not differ significantly from one for either level of paternal exposure to mutagens (Table 1).

The adjusted odds ratio was significantly increased for four paternal exposures: ethylene oxide (OR = 4.7, 95% CI 1.2-18.4), solvents used in the petroleum refineries (OR = 2.2, 95% CI 1.3-3.8), rubber chemicals (OR = 1.5, 95% CI 1.1-2.2) and a subgroup of the former, solvents used in the manufacture of rubber prod-

ucts (OR = 1.9, 95% CI 1.2-2.8; Table 2). Except for ethylene oxide, these exposures are mixtures of several chemicals. From the solvents used in the refineries, gasoline and benzene are suspected to be mutagens. Similarly, from the solvents used in the manufacture of rubber products 1,1,1-trichloroethane and methylene chloride are suspected mutagens. Some of these chemicals also appear in the classification as specific exposures. When paternal exposure to gasoline, benzene, and 1,1,1-trichloroethane were analyzed separately, the odds ratios did not differ significantly from unity.

The risks of spontaneous abortions were also calculated for paternal exposure to lead, carbon disulfide, and heat, which are not mutagens but may adversely affect spermatogenesis. For all these exposures, the odds ratio was below unity but the corresponding confidence interval did not exclude one (Table 3).

In some cases, job title may be a good and specific index of a worker's exposure. For this reason, we calculated the odds ratios of spontaneous abortion by paternal occupation using the 55 occupations included in the exposure classification. The comparison group consisted of wives whose husbands were not exposed to any mutagen. Table 4 lists in descending order the paternal occupations with the highest odds ratios (> 1.20).

Only the results obtained for wives of men employed as rubber product workers reached statistical significance. At the top of the list are also two other occupations in which workers may be exposed to chemicals which we found were associated with an increased risk of abortions (Table 2). These occupations are technical nursing assistants (potentially exposed to ethylene oxide) and oil refinery workers (potentially exposed to solvents of oil manufacture). Other occupations with a high risk of abortion were watchmakers and chimney sweeps.

Discussion

Paternal exposure to certain mutagens may induce spontaneous abortions. We found no difference in the risk of spontaneous abortion between wives of men exposed to any mutagen and wives of men exposed to no mutagen. This may suggest that only a subgroup of mutagens induce spontaneous abortions. Moreover, the mutagenicity of some of the classified agents, such as 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, chloroform, methylene chloride, and the

TABLE 2—Adjusted[a] Odds Ratio of Spontaneous Abortion for Paternal Exposure to Specific Mutagens[b]

Exposure[c] (Level of Exposure)	Number of Spontaneous Abortions	Number of Pregnancies	Odds Ratio	95% Confidence Interval
Ethylene oxide (low)	3	10	4.7*[d]	1.2–18.4
Solvents, petroleum refineries (gasoline, benzene) (moderate or high)	16	93	2.2**[d]	1.3–3.8
Impregnants of wood (arsenic, chromium, creosotes) (low and moderate or high)	5	33	1.9[d]	0.7–5.0
Solvents, manufacture of rubber products (1,1,1-trichloroethane, methylene chloride) (low and moderate or high)	26	180	1.9**	1.2–2.8
Rubber chemicals (low and moderate or high)	34	280	1.5*	1.1–2.2
1,1,1-Trichloroethane (moderate or high)	3	24	1.5[d]	0.4–5.0
Radon (moderate or high)	26	248	1.2	0.8–1.8
Formaldehyde (formaline)				
Low exposure	110	1212	1.1	0.9–1.4
Moderate or high exposure	54	596	1.0	0.8–1.4
Polycyclic aromatic hydrocarbons				
Low exposure	1022	11 970	1.0	0.9–1.0
Moderate or high exposure	142	1619	1.0	0.9–1.2
Nickel and nickel oxides (low)	284	3371	1.0	0.9–1.1
Chromium and chromium compounds (low)	286	3444	1.0	0.9–1.1
Solvents, manufacture of plastic products (styrene) (moderate or high)	24	285	1.0	0.7–1.5
Benzene (low)	55	655	1.0	0.7–1.3
Metals (nickel, chromium, cadmium), basic metal industries and manufacture of metal products (low)	155	1883	1.0	0.8–1.1
Motor gasoline (low)	189	2381	0.9	0.8–1.1
Styrene (moderate or high)	9	120	0.9	0.5–1.8
Trichloroethylene (low and moderate or high)	5	66	0.9[d]	0.3–2.1
Plastic monomers (low)	10	158	0.8	0.4–1.4
Tetrachloroethylene (moderate or high)	3	45	0.7[d]	0.2–2.4
Solvents, manufacture of drugs (chloroform, methylene chloride) (moderate or high)	3	60	0.5[d]	0.2–1.7
Raw materials of glass (arsenic, cadmium) (low)	4	99	0.5[d]	0.2–1.3
Hydrazine (low)	2	51	0.4[d]	0.1–1.7
Solvents, manufacture of printing inks (ethene) (moderate or high)	1	33	0.3[d]	0.0–2.5
Nitroglycol, nitroglyserine, trinitrotoluene (low)	1	34	0.3[d]	0.0–2.3
Solvents, manufacture of glue and gasein (ethene) (moderate or high)	1	35	0.3[d]	0.0–2.3

[a]Adjusted for age (≤24, 25–34, ≥35); socioeconomic status (1 = employers, own-account workers, upper level employees, 2 = lower level employees, students and pupils, 3 = manual workers).
[b]Comparison group was not exposed to any mutagen.
[c]In parentheses are the exposures suspected to be mutagens.
[d]Adjusted for age only.
*$P < .05$, **$P < .01$

TABLE 3—Adjusted[a] Odds Ratio of Spontaneous Abortions for Exposure to Lead, Carbon Disulfide, and Heat[b]

Exposure (Level of Exposure)	Number of Spontaneous Abortions	Number of Pregnancies	Odds Ratio	95% Confidence Interval
Lead (low and high)	352	4476	0.9	0.8–1.0
Carbon disulfide (high)	2	30	0.8[c]	0.2–3.3
Heat (low)	4	109	0.4[c]	0.2–1.2

[a]Adjusted for age (≤24, 25–34, ≥35); socioeconomic status (1 = employers, own-account workers, upper level employees, 2 = lower level employees, students and pupils, 3 = manual workers).
[b]Comparison group was not exposed to any mutagen, lead, carbon disulfide, or heat.
[c]Adjusted for age only.

TABLE 4—Adjusted[a] Odds Ratio of Spontaneous Abortions in the Occupations of the Exposure Classification with Odds Ratio > 1.20[b]

Occupation	Spontaneous Abortions	Pregnancies	Odds Ratio	95% Confidence Interval
Technical nursing assistants	3	22	1.6	0.5–5.6
Rubber product workers	35	281	1.5*	1.1–2.2
Watchmakers	13	102	1.5	0.8–2.7
Chimney sweeps	18	141	1.5	0.9–2.4
Refinery workers	13	111	1.4	0.8–2.5
Smelters, hardeners, temperers in metal industry	4	37	1.4	0.5–3.9
Textile finishers and dyers	14	130	1.3	0.8–2.4
Wire and pipe drawers	5	50	1.2	0.5–3.1
Textile machine setters, operators	22	217	1.2	0.8–1.9

[a]Adjusted for age (≤24, 25–34, ≥35 years).
[b]Comparison group was not exposed to any mutagen.
*$P < .05$.

metals as a group is not well established and depends on the mutation assay used. Thus mutagenicity of the agents such as these is debatable.[15,18] Another example of lack of effect is paternal smoking, one of the most common mutagenic exposures, which appears to have no effect on fertility (time to pregnancy).[19,20]

Of the 25 specific mutagens or groups of mutagens evaluated in this study, paternal exposure to the following four was associated with an increased risk of spontaneous abortion: ethylene oxide, rubber chemicals, solvents used in petroleum refineries, and solvents used in the manufacture of rubber products. Among these, ethylene oxide has been identified as a mutagen by almost all mutation assays, including the dominant lethal assay.[15] Exposure to this chemical has also been associated with spontaneous abortion in women who use the chemical to sterilize hospital instruments.[21] However, our finding of the effects of ethylene oxide is based on a small group of exposed workers. In addition, the job group to which exposure to ethylene oxide was attributed is heterogeneous, and no individual exposures could be confirmed. Rubber chemicals contain several microbial mutagens,[22] and an increased risk of abortion has been observed among women exposed to rubber chemicals.[23] An excessive rate of spontaneous abortion has been found among the wives of workers in a waste water treatment plant of a petroleum refinery[7] and among the wives of workers exposed to organic solvents.[8]

Analyses by occupational title identified only 1 out of 55 occupations, rubber workers, for which the wife's risk of spontaneous abortions was higher than that of wives of men not exposed to mutagens. The wives of men exposed to potentially spermatotoxic but nonmutagenic agents, such as lead, carbon disulfide and heat, did not appear to have an increased risk of spontaneous abortions.

Genetic damage to male germ cells is the only mechanism of male-mediated effects on pregnancy outcome for which supporting evidence is available.[24] Another potential mechanism could be that harmful substances are transmitted to the pregnant woman by contact with clothes or by semen leading to secondary maternal exposure. We were unable to separate the effects of these two routes of exposure.

The misclassification of exposure and pregnancy outcome is an important source of bias in studies of occupational exposure and reproductive outcomes. In this study, misclassification of pregnancy outcome was likely to be small because the data were obtained from hospital records, and spontaneous abortions were medically diagnosed. These data were therefore less susceptible to the information bias which might arise from self-reported data on pregnancy outcome.[11]

In Finland induced abortions are legal. If any induced abortions are reported as spontaneous abortions, we would expect this misclassification to be very small.

It is certain that early spontaneous abortions and a small percentage of induced abortions were not included. The duration of pregnancy before a spontaneous abortion may vary by paternal exposure status. If early fetal losses, which were not included in the study, occurred more often among wives of men exposed to mutagens, the odds ratios reported would underestimate the true relative risk. If the converse were true, the odds ratios would overestimate the true relative risk.

The weaknesses of the study pertain to the potential misclassification of exposure status. Assignment of exposure status was made on the basis of occupational titles and industry. In some cases, these data may not have been sufficiently specific to assess exposure status accurately. Consequently, some exposed persons may have been classified incorrectly as unexposed, and this could have resulted in low sensitivity of the exposure assessment. Conversely, occupational categories may have been so broad that unexposed persons may have been classified as exposed, inducing low specificity. Random error in the classification of exposure status (nondifferential misclassification) may have diluted the effects of exposures and may explain the absence of associations in this study.

Although census data do not provide completely accurate exposure information, care was taken to assess exposure as accurately as possible. First, analyses were carried out in the time period close to the date of the censuses to allow minimal

time for change in occupation. Second, exposure status was determined independently of reproductive outcome. Third, the job exposure classification rather than mere job title was used to assign exposure status; in some cases it was possible to quantify the exposure.

No information was available on other potential confounding factors such as previous spontaneous abortions or the use of alcohol or smoking. Probably the adjustment of the socioeconomic status has partly controlled the effect of smoking and alcohol drinking, as they vary by social class.

This large study showed no overall excess of spontaneous abortions in women whose husbands were exposed to mutagens in general compared with those whose husbands were not exposed to mutagens. However, excesses were observed among wives of men employed as rubber products workers and of men exposed to ethylene oxide, solvents used in petroleum refineries, rubber chemicals, and solvents used in the manufacturing of rubber products. Many comparisons were made in this study, and some of the associations probably reflect chance alone. Thus, our findings are only suggestive. This emphasizes the need to base inferences on biologic plausibility and on the evidence accumulated from this and other studies. Although there is some biological rationale for these findings, they need to be confirmed by studies in which individual exposures can be assessed directly. □

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